UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/197,056	11/20/98	RUSSELL S	3789/77553

HM22/1226

KATHLEEN M WILLIAMS
BANNER AND WITCOFF LTD
28TH FLOOR
28 STATE STREET
BOSTON MA 02109

EXAMINER	
WILSON, M	
ART UNIT	PAPER NUMBER
1633	14

DATE MAILED: 12/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/197,056	RUSSELL ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-3-00, paper number 12, has been entered.

Applicant's arguments filed 10-3-00, paper number 13, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim 10 has been canceled. Claims 1-9 and 11-18 are under consideration in the instant application.

Specification

1. The abstract of the disclosure is objected to because it contains legal phraseology such as "comprising" and "said". Correction is required. See MPEP § 608.01(b).

2. The description of Fig. 2A, 2B and 3 (page 7, line 12) is not adequate because it does not describe Fig. 3 individually and because it does not adequately describe the FACS data displayed in Fig. 2A, 2B or 3. It cannot be determined from the description on page 7 how the data in each figure differs or what conditions are being displayed (i.e. cell type, protein detected by FACS). Page 26, lines 29 through page 27, line 9 more accurately describes Fig. 2A and 2B.

Claim Rejections - 35 USC § 112

3. Claims 1-9 and 11-18 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating the expression of a nucleic acid sequence encoding an immunogenic peptide *in vitro* comprising a) transfecting a cell with a nucleic acid sequence encoding an immunogenic peptide operably linked to a tetracycline regulatable promoter and b) regulating the expression of the sequence by altering the tetracycline concentration to which the cell is exposed such that expression of the immunogenic peptide is altered, does not reasonably provide enablement for a method of regulating the expression of a nucleic acid sequence using a non-tetracycline regulatable system, or regulating the nucleic acid *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For clarification, the examiner considers an immunogenic polypeptide any protein which induces an immune response such as GM-CSF or a chimeric T-cell receptor as disclosed in the specification (page 7, line 24).

Therapy

Therapeutic and anti-tumor embodiments as in claims 11 and 12 are not enabled. At the time of filing it was unpredictable what vector, promoter, gene of interest, level of gene

expression, target tissue, dosage or route of administration were required to obtain any therapeutic effect using gene therapy (Ross of record, Sept. 10, 1996, Human Gene Therapy, Vol. 7, page 1781-1790; page 1786, column 1, paragraph 2; page 1786, column 1, paragraph 2; Verma of record, Sept. 18, 1997, Nature, Vol. 389, pages 239-242; see page 239, 3rd column, line 10; page 239, column 1, line 16). It was not within the realm of routine experimentation for one of skill in the art to determine the parameters required to obtain any therapeutic or anti-tumor effect using gene therapy.

The specification demonstrates transfecting Jurkat cells with a vector encoding a chimeric T-cell receptor operably linked to the tetracycline operator and encoding tTA. The expression of the T cell receptor is increased by decreasing the concentration of tetracycline *in vitro* (page 31). Applicants do not teach the level of gene expression, route of administration, vector or promoter of cells made by such a method that are therapeutic. Nor does the specification provide adequate guidance how to regulate expression of the cells once they are delivered to the mammal. The specification does not teach the level of expression of chimeric TCR or any other protein required to obtain a therapeutic or anti-tumor effect or the level of expression of tTA required to regulate gene expression *in vivo*. The examiner does not doubt the possibility of obtaining a therapeutic effect or anti-tumor effect using gene therapy. However, given the guidance provided in the specification taken with the unpredictability in the art, it would have required one of skill in the art undue experimentation to determine the parameters required to obtain a "therapeutic effect" or "anti-tumor effect" or to regulate gene expression *in vivo* at the time the invention was made.

Applicants argue the specification teaches parameters including the vectors, promoters and dosage required for therapy. A list of vectors and promoters does not overcome the unpredictability in the art by teaching the particular combination of vectors, promoters and dosage required for therapy. Applicants provide information known in the art at the time of filing regarding obtaining stable transfection of a construct *in vitro*, regulating expression of a marker gene in transgenic mice and treating tumors using HSV-TK. Regulating a transgene in transgenic mice does not correlate to the instant invention because the instant invention requires administration of cells expressing the transgene followed by altering tetracycline concentrations while the transgenic mouse expresses the transgene in all of the cells. The specification does not teach how to target the tetracycline to cells administered to a mammal as claimed in the instant invention. The example of obtaining a therapeutic effect using a gene encoding HSV-TK does not correlate to the instant invention because HSV-TK is a gene that can be used to kill the cell while the chimeric TCR is used to "target T cells toward native antigens" (page 2, line 19). It is not clear that the level of expression of HSV-TK (or any of the other proteins in the references provided) required to obtain a therapeutic effect is equivalent to the level of expression of the chimeric TCR required to obtain a therapeutic effect. It is noted that in the references provided wherein a therapeutic effect is obtained, gene expression does not result in any therapeutic or anti-tumor effect but is limited to a specific therapeutic or anti-tumor effects, e.g. tumor regression. Overall, applicants have not provided the amount of tetracycline or level of chimeric TCR required to obtain a therapeutic effect. Given the unpredictability in the art at the time of filing

taken with the guidance provided in the specification, it would have required one of skill undue experimentation to determine the vector, promoter, dosage, level of expression and regulation of expression required to obtain a "therapeutic" or "anti-tumor" effect at the time of filing.

Verma of record (Sept. 18, 1997, Nature, Vol. 389, pages 239-242) states the *in vivo* approach of gene therapy is unpredictable because of an inability to deliver genes efficiently and to obtain sustained expression and that there is still no single outcome that we can point to as a success story (page 239, 3rd column, line 10; page 239, column 1, line 16). Verma correlates to cancer treatment in that the reference discusses the unpredictability in determining the vector required to obtain a therapeutic level of gene expression using gene therapy. While Verma suggests that adenoviral vectors encoding immunomodulatory gene may be used to augment tumor killing, Verma does not teach that the augmented tumor killing is *in vivo* or provide the parameters required to obtain such an effect *in vivo*. The overall message of Verma is that it is unclear what vector and promoter are required to obtain therapeutic results using gene therapy.

Alvarez-Vallina of record (March 1, 1999, Human Gene Therapy, Vol. 10, pages 559-563) teach that activation in the Jurkat model of expressing chimeric TCR parallels the activation of normal T-cells but that analysis of T-cell response over a period of time is required to determine the applicability of cells expressing chimeric TCR (page 562, column 2, line 1). While cells expressing chimeric TCR *in vitro* were known in the art and taught in the specification, the specification does not teach how to use such cells to express chimeric TCR *in vivo* to therapeutic levels by teaching the level of expression required *in vivo*, or the dosage or route of delivery or

regulation required to obtain a therapeutic effect using a chimeric TCR. Examples 1 and 2 are *in vitro* and do not correlate to *in vivo* embodiments because it is not clear that the level of expression of chimeric TCR obtained *in vitro* would have any therapeutic effect. Given the unpredictability in the art regarding how to use cells expressing chimeric TCR taken with the guidance in the specification, it would have required one of skill undue experimentation to determine the parameters required to use a chimeric TCR to obtain a therapeutic or anti-tumor effect as claimed.

Regulation system

The specification does not enable regulating the expression of a polypeptide by altering the concentration of regulatory drug after the cell has been administered (claim 14). The specification does not teach how to administer or alter tetracycline in a mammal such that the transfected cells would be regulated after the cells have been introduced into the mammal. Applicants example on page 11 does not relate to the claim because the concentration of tet is not altered after the cell is introduced into the mammal. In addition, the claims are not limited to transfecting the cells *in vitro*, culturing the cells *in vitro* with tet, removing the tet *in vitro* and administering the cells to a mammal. Thus, the method of regulating the expression of the protein is not enabled as broadly claimed.

Other

Claims 4-6 are not enabled for regulating gene expression in a mammal that has made an immune response to the immunogenic peptide prior to administration of the a cell. While page 22, lines 5-12 suggest such an approach, the specification does not provide adequate guidance what applicants consider the appropriate immune response, circulating antibodies or immunocompetent memory cells which react with the immunogenic polypeptide or how to detect such parameters. The specification does not teach how to regulate the expression of an immunogenic polypeptide in a mammal with an immune response to the immunogenic peptide or how to use such a method. The claims do not provide a nexus between a method of regulating a gene which results in a desired immune response. The preamble should reflect the substance of the claim.

Claims 7-9 are not enabled as written because there is no nexus between the preamble and body of the claims. Inhibition of the polypeptide *in vitro* as recited in claim 7 is not regulating the expression of a polypeptide in a mammal as in the preamble of claim 1. Claim 7 does not recite when the tetracycline is removed to allow expression; therefore, the claim encompasses regulating the expression of a protein in a mammal by altering tetracycline levels while it is within the mammal. However, the specification does not provide any guidance how to alter tetracycline levels while the cells are in the mammal.

The specification does not enable using viral vectors (claim 13). While viral vectors were known in the art and mentioned in the specification, given the unpredictability in the art regarding the vector used to obtain the desired result *in vivo* taken with the lack of guidance in the

specification regarding how to regulate gene expression *in vivo* using viral vectors, applicants have not enabled using viral vectors to regulate gene expression in a mammal as claimed.

4. Claims 1-9 and 11-18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 11-13 and 18 are indefinite because the claim 1 is directed to "regulating the expression of a nucleic acid sequence" but only results in expression of a nucleic acid sequence. It is unclear in claim 18 if regulation of gene expression ever occurs because "so as to regulate..." is an intended use and may not occur. Replacement of the preamble with "A method of altering the expression of a nucleic acid sequence in a mammal" in combination with a final step "wherein the expression of the nucleic acid sequence is altered in the mammal" is suggested.

Claims 1-9 and 11-13 are indefinite because the preamble of claim 1 and claims 11 and 12 state the polypeptide is "immunogenic in the mammal", but the body of claim 1 does not require that the polypeptide is "immunogenic". It is unclear whether applicants intend the scope of polypeptides encompassed in the claim to be a particular "immunogenic" species of polypeptides or any polypeptide.

Claims 1-9, 11-13 and 18 are indefinite because the phrase "altering the concentration of tetracycline...to which the cells [leukocyte] is exposed" is indefinite (claims 1 and 18) as it relates

to the step of administering the cells. In particular, it is unclear whether the concentration of tet is altered before or after administering the cells to the mammal.

Claims 4-9 are indefinite because it is unclear whether "said polypeptide" or "the polypeptide" refers to an "immunogenic polypeptide" as in the preamble of claim 1 or a generic "polypeptide" in the body of the claim. It is unclear if applicants are attempting to characterize the mammal or to add a step to the method. A mammal cannot have an immune response to a polypeptide (claim 4), circulating antibodies which react with a polypeptide (claim 5), immunocompetent cells (claim 6) without prior exposure to the polypeptide. However, prior exposure to the polypeptide is not required in the claim. It is unclear whether the mammal has been exposed to the same polypeptide encoded by the vector and whether the exposure was prior to administration of the cells.

The phrase "the mammal" in claim 1, lines 2 and line 3 lacks antecedent basis.

Claim 17 is indefinite because the phrase "said nucleic acid coding sequence" lacks antecedent basis in the claim.

Claim 18 is indefinite because the phrase "the isolated leukocyte" lacks antecedent basis in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 14, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Shockett (Shockett et al, July 1995, PNAS, USA, Vol. 92, pages 6522-6526).

Shockett teaches transducing fertilized eggs with a vector encoding luciferase under the control of the tet operator (page 6523, Fig. 1 and Fig. 1 legend; page 6525, paragraph bridging columns 1 and 2). The eggs were implanted into a pseudopregnant female which is considered equivalent to introducing a cell into a mammal as claimed. Tetracycline was removed which is equivalent to "altering the concentration of tetracycline" as claimed. Shockett also teaches transducing NIH 3T3 cells with a vector encoding luciferase under the control of the tet operator, selecting transformed cells, mixing the cells with media and altering the concentration of tetracycline (page 6524, column 2, first full paragraph; page 6524, Fig. 2 and Fig. 2 legend). Media is considered a physiologically acceptable diluent (claims 16 and 17). Luciferase is an immunogenic polypeptide (claim 14) because it is a non-mammalian protein that is recognized by the immune system of mammals as foreign.

Claims 14 and 16 do not differ from the cells of Shockett because the cells have the same nucleic acids as those claimed and because the phrase "such that expression... is controlled by altering the concentration of tetracycline..." (claim 14) does not alter the structure of function of the cell in way that differs from the cells of Shockett. It is noted, however, that expression of

luciferase is controlled in the eggs or 3T3 cells by altering the concentration of tetracycline. The phrase "after introduction to a mammal" in claim 14 is an intended use and does not bear patentable weight on the cell claimed because it does not alter the structure or function of the cells. Thus, Shockett anticipates the claims.

6. Claims 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoffmann (Hoffmann et al., PNAS, USA, May 1996, Vol. 93, pages 5185-5190).

Hoffmann teaches transfecting lymphocytes with a retroviral vector encoding LacZ operatively linked to the tet operator and also encoding the tetR-VP16 (page 5186, column 2, 2nd paragraph; page 5187, column 1, first full paragraph, line 90; page 5189, col. 1, last line). LacZ is considered an immunogenic polypeptide (claim 14) because it is a bacterial protein that is recognized by mammals as foreign. The lymphocytes taught by Hoffmann are "leukocytes" as claimed. The media used to culture the cells in Hoffmann is considered a physiologically acceptable diluent (claims 16 and 17). Growing cells in the tetracycline analogue Dox and detecting LacZ expression (page 5187, column 1, 10 lines from the bottom) is equivalent to selecting cells successfully transformed (claim 17). VP16 is equivalent to a tetracycline-sensitive DNA-binding expression-regulating polypeptide (claim 18) because it binds DNA, is sensitive to tet and regulates gene expression. The limitation of "so as to regulate expression of the coding sequence" (claim 18) is an intended use and does not necessarily occur.

Claims 14 and 16 do not differ from the cells of Hoffmann because the cells have the same nucleic acids as those claimed and because the phrase "such that expression... is controlled by

altering the concentration of tetracycline..." (claim 14) does not alter the structure of function of the cell in way that differs from the cells of Hoffmann. It is noted, however, that expression of LacZ is controlled in the cells by altering the concentration of tetracycline. The phrase "after introduction to a mammal" in claim 14 is an intended use and does not bear patentable weight on the cell claimed because it does not alter the structure or function of the cells. Therefore, Hoffmann anticipates the claims.

7. Claims 14-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Cooke (Cooke et al., Feb. 1997, J. General Virol., Vol. 78, pages 381-392).

Cooke teaches transfecting human T cell lines and mouse macrophages with a vector encoding *nef* operably linked to a CMV/tetracycline operator promoter and a vector encoding tTA (page 382, col. 2, first and second full paragraphs; page 383, Fig. 1 and legend of Fig. 1). *Nef* is considered an immunogenic polypeptide (claim 14) because it is a viral protein that is recognized by mammals as foreign. T cells are "leukocytes" as claimed. The media used to culture the cells is considered a physiologically acceptable diluent (claims 16 and 17). Growing cells in the tetracycline and detecting *nef* expression is equivalent to selecting cells successfully transformed (claim 17). The phrase "such that expression... is controlled by altering the concentration of tetracycline..." (claim 14) does not alter the structure of function of the cell in way that differs from the cells of Hoffmann. It is noted, however, that expression of *nef* is controlled in the cells by altering the concentration of tetracycline. The phrase "after introduction to a mammal" in claim 14 is an intended use and does not bear patentable weight on the cell

claimed because it does not alter the structure or function of the cells. Therefore, Cooke anticipates the claims.

Claim Rejections - 35 USC § 103

8. Claims 1-3 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooke (Cooke et al., Feb. 1997, J. General Virol., Vol. 78, pages 381-392).

Cooke teaches transfecting human T cell lines and mouse macrophages with a vector encoding *nef* operably linked to a CMV/tetracycline operator promoter and a vector encoding tTA (page 382, col. 2, first and second full paragraphs; page 383, Fig. 1 and legend of Fig. 1). tTA is equivalent to a tetracycline-sensitive DNA-binding expression-regulating polypeptide because it binds DNA, is sensitive to tet and regulates gene expression. Cooke does not teach administering the cells to a mammal or altering the tet concentration. However, Cooke suggests administering the cells to a mammal and altering the tet concentration (page 390, col. 1, last paragraph; page 390, col. 2) which is all that is required of the claim.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

9. Claims 1-3, 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann (Hoffmann et al., PNAS, USA, May 1996, Vol. 93, pages 5185-5190).

Hoffmann teaches transfecting lymphocytes with a retroviral vector encoding LacZ operatively linked to the tet operator and also encoding the tetR-VP16 (page 5186, column 2, 2nd

paragraph; page 5187, column 1, first full paragraph, line 90; page 5189, col. 1, last line). Lymphocytes are considered leukocytes. TetR-VP16 is considered a "tetracycline-sensitive DNA-binding expression-regulating polypeptide" because it is binds DNA and regulate LacZ expression according to the level of tetracycline present. Removing Dox (a tetracycline analogue) from the transduced cells (page 5187, column 1, 10 lines from the bottom) is considered equivalent to altering the concentration of a tetracycline analogue. Hoffmann does not expressly teach administering the cells to a mammal.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the cells of Hoffmann to a mammal because Hoffmann suggests delivering the cells to a mammal (page 5190, col. 1, line 1 through the end). Therefore, it would have been obvious to one of skill in the art at the time the invention was made to administer the cells of Hoffmann to a mammal and to alter the concentration of a tetracycline analog as claimed.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 4-6 appear to be free of the prior art of record because the prior art of record does not teach or suggest introducing a cell expressing a polypeptide into a mammal wherein the mammal has an immune response to the polypeptide, circulating antibodies that react to the polypeptide or immunocompetent memory cells specific for the polypeptide. Claims 7-9 appear to be free of the prior art of record because the prior art of record does not teach or suggest

reaching a maximum level of polypeptide expression after 2 days or inducing expression after 2 days by administering tetracycline as claimed. Claims 11 and 12 appear to be free of the prior art of record because the prior art of record does not enable therapeutic or anti-tumor embodiments.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

Deborah Clark

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600